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Major Side Effects of Antipsychotic Drugs

K. D. Charalampous, MD and G. A. Keepers, MD
Houston, Texas

Since the introduction of phenothiazines into clinical practice in 1952, over 250 million people have received these drugs for the treatment of psychotic states. In addition to the phenothiazines, five other classes of neuroleptic medications are now in use: butyrophenones, thioxanthenes, dihydroindolones, diphenylbutylpiperidines, and dibenzoxazepines. Besides their use in the treatment of psychosis, these drugs have been used in the treatment of anxiety, depression, nausea, alcoholic withdrawal, and pain, and are often administered in combination with other medications. Through the use of these drugs, many psychotic patients have been able to move back into the community, and the family physician is coming into contact with more patients on maintenance dosages of neuroleptics. He/she may wish to prescribe these drugs or may, in the treatment of a medical problem, need to prescribe other medication to an individual already receiving neuroleptics. It is important, therefore, for the family physician to be aware of the side effects of these drugs and of complications which can arise when neuroleptics are given in combination with other families of drugs.

The actions of neuroleptic agents are amazingly ubiquitous and involve every organ system. Centrally, they are dopamine-blocking agents, affecting neural transmission from the cortex to the brain stem and even hypothalamic control of pituitary function. Peripherally, they are both potent alpha adrenergic-blocking agents and anticholinergic agents affecting the cardiovascular system and the autonomic nervous system. There are a host of other actions including antiemetic, antihistaminic, and antipyretic. The antipsychotics, nevertheless, have a high therapeutic index and are remarkably safe agents. Death from an overdose is a rare event. Most known side effects are extensions of the pharmacological actions of these drugs, the most important being those on the central nervous system, endocrine system, and cardiovascular system. In addition, there are a few toxic and idiosyncratic effects unrelated to the antipsychotic actions or to the interactions resulting from their concomitant prescription with other medications. This article explores the major side effects of these drugs (Table 1) and their interactions with other medications

From the Department of Psychiatry, Baylor College of Medicine, Houston, Texas. Requests for reprints should be addressed to Dr. K. D. Charalampous, Department of Psychiatry, Texas Tech University School of Medicine, P.O. Box 4569, Lubbock, TX 79409.

(Table 2) beginning with the central nervous system.

Central Nervous System Effects

The totality of actions of the antipsychotic drugs within the central nervous system is not yet thoroughly understood. The antipsychotics appear to affect all neurotransmitters but particularly influence levels of dopamine and norepinephrine. By blocking central dopaminergic transmission, secondary extrapyramidal side effects are produced. Dopamine, norepinephrine, and other neurotransmitters are also implicated in the electroencephalographic (EEG) and psychobehavioral changes, but the mechanisms are less well understood.

All phenothiazines other than promazine and prochlorperazine lower the seizure threshold. Haloperidol also lowers the seizure threshold and its effects on the EEG are similar to those of the phenothiazines. These agents produce slowing of the EEG and increased occurrence of theta waves. The variability of frequencies decreases, while voltage and burst activity increase. The piperazine phenothiazines differ slightly in that they produce increased alpha wave activity as well.

In nonpsychotic individuals, the antipsychotics may impair vigilance on various psychomotor tests, may interfere with complex intellectual functions, and may reduce spontaneous motor activity. In psychotic patients, neuroleptic medications produce psychomotor slowing, emotional quieting, and affective indifference, termed the neuroleptic activity by Delay and Deniker.[1] Additionally, many neuroleptics produce sedation, although there is no correlation between the sedative property and therapeutic effectiveness of the antipsychotic drugs. The sedative effect may be useful in the treatment of anxious or agitated patients. Tolerance develops rapidly to the sedative effects of these medications but not to the neuroleptic effects. Mild withdrawal symptoms can occur.

The administration of antipsychotic drugs may induce several neurological syndromes of which three—parkinsonism, akathisia, and dystonia—are acute, and one—tardive dyskinesia—is chronic. Haloperidol and the piperazine derivatives of phenothiazines seem to produce the acute syndromes more frequently than other antipsychotics, while the dibenzoxazepines and thioxanthenes have the lowest incidence of these side effects. Severe extrapyramidal side effects, sometimes delayed by several days, can also occur after depot phenothiazines; however, patients maintained on fluphenazine decanoate develop fewer extrapyramidal side effects than those on fluphenazine enanthate.

Parkinsonism is probably due to a functional dopamine deficiency. It may be indistinguishable from idiopathic parkinsonism. The most noticeable signs are tremor at rest and rigidity; "pill rolling" movements are common; and there is a generalized slowing of volitional movements and a mask-like facies. The syndrome responds to reduction of dosage, to anticholinergic agents, and according to a recent report, to amantadine.[2]

The second acute type, akathisia, is not a specific movement or symptom; it refers rather to an inability of the patient to remain quiescent. The patient feels a compelling need to move, which he may find impossible to control, and this movement may be mistaken for psychological agitation. The cause of akathisia is not known. It has been shown that previous hyperthyroidism or hyperparathyroidism increases the risk of acquiring the disorder. Akathisia responds less frequently to anticholinergics than other extrapyramidal side effects do; its treatment, therefore, may require reduction in antipsychotic dosage and the use of diazepam.

The third acute syndrome, dystonia, is a common side effect that may occur early during antipsychotic treatment. It is most often seen in children and young adults. Torticollis and facial grimacing are present and may be accompanied by oculogyric crises. Dystonia is thought to be due to transient dopaminergic hyperactivity and is occasionally mistaken for hysteria or seizures, but can be readily differentiated from them by its response to anticholinergic agents. The dystonia is self-limited and will generally abate without treatment. Severe symptoms may be treated with intramuscular anticholinergics (eg, benztropine 1 to 2 mg), intravenous caffeine sodium benzoate (500 mg), or intramuscular diphenhydramine (50 mg).

While clinical management for these three acute

Table 1. Common Side Effects of Antipsychotic Drugs

Organ System	Drug Family	Side Effects
Autonomic	All antipsychotics	anticholinergic: dry mouth blurring of vision urinary retention constipation
	Phenothiazines	perspiration
Neurologic	Phenothiazines Butyrophenones	lowered seizure threshold
	All antipsychotics	extrapyramidal reactions: parkinsonism akathisia dystonia
	All antipsychotics	tardive dyskinesia
Endocrinous	All antipsychotics	hypothalamic susceptibility to hyperpyrexia and hypopyrexia appetite increase
	All antipsychotics	galactorrhea
	All antipsychotics	amenorrhea or dysmenorrhea
Cardiovascular	Phenothiazines	ECG changes
	Phenothiazines	arrhythmias
	Phenothiazines	hypotension
	Phenothiazines	cardiomyopathy
Dermatologic	All antipsychotics	skin rash
	Phenothiazines	photosensitivity
	Phenothiazines	pigmentation
Ocular	Phenothiazines	lens pigmentation
	Phenothiazines	pigmentary retinopathy
Hematologic	All antipsychotics	leukopenia and agranulocytosis
Hepatic	phenothiazines	obstructive jaundice

Table 2. Antipsychotic Drug Interactions

Antipsychotic Drug	Other Medication	Interaction
Phenothiazines Butyrophenones Thioxanthenes	Antiparkinsonian drugs	Interference with antipsychotic efficacy Increased risk of tardive dyskinesia
Phenothiazines Butyrophenones Thioxanthenes	Anticholinergics Tricyclic antidepressants	Additive anticholinergic effects Aggravation of tardive dyskinesia
Phenothiazines Butyrophenones Thioxanthenes	Estrogens	Increased plasma levels of antipsychotic drugs Increased risk of extrapyramidal reactions
Phenothiazines	Barbiturates Lithium	Reduced plasma levels of antipsychotic drugs
Phenothiazines Butyrophenones Thioxanthenes	Antihypertensives	Additive hypotensive effect
Chlorpromazine	Guanethidine and false transmitter antihypertensives	Rise in blood pressure
Phenothiazines Butyrophenones Thioxanthenes	Sympathomimetics	Pressor effect inhibited
Phenothiazines Butyrophenones Thioxanthenes	Norepinephrine	Retains hypertensive effect
Phenothiazines Butyrophenones Thioxanthenes	CNS Depressants	Additive CNS depression
Chlorpromazine	Anticoagulants	Potentiate anticoagulant activity

conditions has been mentioned, the ideal treatment for extrapyramidal symptoms is still uncertain. In the past, antiparkinsonian agents were often coadministered with neuroleptics in an effort to prevent neurological side effects. Patients were often maintained on these regimens for years. It is important to note, therefore, that numerous reports indicate only a minority of patients develop a recurrence of symptoms when the antiparkinsonian agent is stopped. The relapse rate has varied among studies: one reported a 10 percent rate,[3] whereas, another reported a 27 percent rate.[4] A recent study by McClelland and colleagues in Britain[5] of 100 inpatients found an extremely low incidence (four percent) of the recurrence severe enough to require reinstitution of antiparkinsonian agents. Other studies found no need for the chronic use of antiparkinsonian agents, even with depot phenothiazines.[6]

Furthermore, the antiparkinsonian agents are not benign. Undesirable anticholinergic effects are relatively common and may combine with those caused by the phenothiazines to give a significant incidence of blurred vision, gastric irritability, dizziness, and lethargy. A toxic psychosis, a variant of the "central anticholinergic syndrome," may result; and the antiparkinsonian agents may interfere with the actions of the neuroleptics. Studies in 1972[7] showed that benztropine may reverse some of the therapeutic effects of haloperidol. Subsequent experiments have demonstrated that trihexyphenidyl reduces the plasma levels of chlorpromazine.[8]

The routine prescription of antiparkinsonian agents with antipsychotic drugs is, therefore, to be avoided. Extrapyramidal side effects should be treated only when they are of clinical significance. The initial treatment approach consists of decreasing the dose of the offending neuroleptic drug, or prescribing an alternate neuroleptic. These approaches may not be practical in patients with uncontrollable psychotic symptoms. The use of an antiparkinsonian agent may then be unavoidable. It should be remembered, however, that such treatment may increase the patient's discomfort as well as decrease the effectiveness of his antipsychotic management. Since there is a diminution of extrapyramidal side effects after the first three months of treatment, withdrawal of antiparkinsonian medication should be attempted after this period.

In view of the undesirable properties of antiparkinsonian drugs, the recent studies of amantadine are encouraging. Amantadine is a putative dopaminergic compound which has proven effective in the treatment of idiopathic parkinsonism. It does not have any appreciable anticholinergic activity. Controlled studies found amantadine to be comparable to standard antiparkinsonian agents (benztropine and trihexyphenidyl) but with fewer side effects.[1,9]

In contrast to the acute syndromes of parkinsonism, akathisia, and dystonia, tardive dyskinesia is a late occurring neurological syndrome which is associated with chronic administration of phenothiazines. It is characterized by rhythmical involuntary administration of the tongue, face, mouth, and jaw, sometimes accompanied by choreoathetoid movements of the extremities. The syndrome occurs more frequently in the elderly and in those with prior neurological deficit. Risk has been related to total intake of neuroleptics. Symptoms may be masked by increased dosage of neuroleptics; after discontinuation of the neuroleptic, however, symptoms may persist indefinitely or even worsen. Antiparkinsonian agents worsen tardive dyskinesia and may increase the incidence of this disorder when given concurrently with neuroleptics.

The production of tardive dyskinesia is related to the activity of dopamine at certain striatal receptor sites. By analogy with L-dopa-induced dyskinesia and with Huntington chorea, it appears that tardive dyskinesia may be produced by increased responsiveness of dopamine receptor sites as a result of neuroleptic-induced denervation hypersensitivity.

Numerous pharmacological treatments of this condition have been attempted. The medications tested include reserpine, tetrabenazine, pimozide, haloperidol, thiopropazate, perphenazine, lithium, methyldopa, alpha methyl paratyrosine, amantadine, papaverine, physostigmine, deanol, pyridoxine, tryptophan, and 5-hydroxytryptophan. No single drug has emerged as the agent of choice. Most clinicians, therefore, recommend that patients on long-term antipsychotic therapy be carefully and frequently examined so that this disorder can be detected as early as possible. Drug holidays may reduce the risk of this disorder and may also reveal dyskinesia at an earlier stage. When the dyskinesia is

first recognized, the antipsychotic drug should be discontinued. If further pharmacological management is required for psychotic behavior, a change to a drug with few extrapyramidal side effects should be considered. This approach will lead to the resolution of symptoms in at least some cases. If this approach is unsuccessful, it might then be appropriate to challenge patients with different categories of drugs including cholinomimetic drugs and dopamine-blocking agents. The results from such a therapeutic regimen could then be used to plan a longer, more extensive course of therapy.

Endocrinous and Metabolic Effects

Most antipsychotic medications have metabolic or endocrinous effects. Chlorpromazine's actions have been the most thoroughly explored, but it is presumed that other antipsychotics produce similar effects. The alterations in endocrine function are mediated through the drug's action on the hypothalamus.

Miscellaneous and complex side effects are produced by the actions of antipsychotic drugs on the hypothalamus. These agents may affect hypothalamically controlled temperature regulation, rendering patients vulnerable to hypothermia or hyperthermia. Disturbances in the hypothalamic control of appetite are likely responsible for the weight gain seen in some patients taking neuroleptics. Chlorpromazine and other antipsychotics decrease the secretion of growth hormone, an effect which has been utilized in the treatment of acromegaly. Serum prolactin levels have been shown to be elevated three- to fourfold in patients receiving neuroleptics. This elevation is believed to result from the inhibition of dopamine receptors in the hypothalamopituitary axis, preventing dopamine-mediated inhibition of prolactin release. Some progress has been made in the treatment of the resultant galactorrhea with brom-ergocryptine.[10] Administered in the dosage of 5 mg/day, this drug significantly reduces galactorrhea. Amenorrhea and dysmenorrhea may also be produced in a significant portion of women on neuroleptics due to interference with the pituitary regulatory sex hormones.

Cardiovascular Effects

Effects on the cardiovascular system have been reported with all antipsychotics though more frequently with the phenothiazines. Complex, incompletely understood effects are produced through direct actions on the heart and blood vessels and through responses mediated by autonomic reflexes and the central nervous system. The most important mechanisms of action are alpha adrenergic blockade and a direct depressant action on the myocardium. Prolonged ventricular repolarization is observed frequently in patients receiving high doses of thioridazine. Fasting and potassium administration reverse this change while oral glucose load exacerbates it. Prolonged repolarization can lead to reentry arrhythmias, a cause of sudden death in treated patients. Reported clinical effects of the antipsychotics on the cardiovascular system include acute hypotension, ECG changes, arrhythmia, infarction, cardiomyopathy, and cardiac failure. These effects are dose dependent, more frequent with the aliphatic phenothiazine derivatives, more likely to occur with chronic administration (except for hypotension), and more apt to occur in patients susceptible to or having cardiovascular disease. Additionally, cardiovascular toxicity is more likely to occur with acute overdosage and with polypharmacy.

While the parenteral administration of phenothiazines may cause an acute drop of 40 mmHg or more in blood pressure, the average fall in blood pressure is much smaller and shock is a rarity. When it occurs it indicates a preexisting circulatory lability and should prompt a search for pheochromocytoma. Reports of sudden death due to coronary thrombosis during phenothiazine treatment have been attributed to this effect. Moderate hypotension can usually be managed by keeping the patient prone and by elevating the legs. Severe phenothiazine hypotension can be treated with norepinephrine or dopamine and should not be treated with epinephrine, since

epinephrine administration in the presence of these alpha adrenergic-blocking agents lowers blood pressure.

Chlorpromazine and other neuroleptics can produce a variety of ECG alterations, including T wave blunting, ST depression, and Q-T segment lengthening. It has been proposed that these ECG abnormalities are a benign disturbance of myocardial repolarization correctable by administration of a potassium salt. Nonetheless, several cases of ventricular arrhythmia and sudden death have been reported in patients treated with antipsychotics. Third-degree heart block with ventricular tachycardia has been reported in several patients taking high doses of thioridazine; sudden death in patients taking chlorpromazine has been reported by several authors. A review by Leetsma and Koenig in 1968 of 54 cases of sudden death during phenothiazine treatment suggested that drug-induced arrhythmia rather than atherosclerotic heart disease was responsible for death.[11] Autopsy studies have shown some abnormalities in the myocardium, suggesting a possible mechanism for arrhythmias. Hollister and Kosek[12] have reported pigment deposition in the myocardium, and Alexander and coworkers[13] have reported pigmentation as well as changes in the arterioles of patients who die of phenothiazine overdosage.

The weight of the evidence indicates that the phenothiazines, especially the aliphatic and piperidine derivatives, can have cardiotoxic effects. It is essential, therefore, that physicians prescribing these drugs periodically evaluate their patients' cardiac status. If ECG abnormality or cardiomegaly is found, the physician should reassess the patient's psychiatric status to determine if continued drug treatment provides sufficient benefit to outweigh the risk involved.

Idiosyncratic and Toxic Effects

Toxic and idiosyncratic reactions have been reported with all antipsychotic drugs. The most complete information, however, comes from studies of the phenothiazines and particularly of chlorpromazine. The major reactions of this type affect the skin, eyes, bone marrow, and liver. The effects on these organ systems are thought to be due to hypersensitivity to the particular neuroleptic; often switching to a drug from a different class results in disappearance of symptoms.

Four types of dermatological reactions occur with neuroleptic medications. About five percent of the patients treated develop a hypersensitivity reaction between the first and fifth week of treatment, which may be urticarial, edematous, petechial, or maculopapular. Withdrawal of medication produces clearing, and the condition may not reoccur upon reinstitution of therapy. Photosensitivity is another problem that may develop, necessitating an effective sunscreen, such as those containing para-aminobenzoic acid. Others receiving high doses of phenothiazines administered for a long time have developed abnormal skin pigmentation. While chlorpromazine has been reported as producing this reaction most frequently, other phenothiazines have also been implicated. The skin in this condition is pigmented grayish blue in exposed areas and the dermis contains melanin deposits throughout the corium. Finally, contact dermatitis may develop in personnel who handle antipsychotics, especially phenothiazines.

Eye changes are a common side effect and have been extensively documented in retrospective studies. In combined series totaling some 1,554 patients without any skin hyperpigmentation, approximately 30 percent of the patients had drug-related eye lesions. Both lenticular opacities, which are granular deposits in the axial portion of the anterior capsule, and corneal changes were seen. In most patients no impairment of visual acuity resulted. However, some patients on very high doses of chlorpromazine for a number of years have a reduction of visual acuity due to cataracts, which one group[14] found to be reversible if the patient was switched to another drug and was treated with d-penicillamine. Pigmentary retinopathy has also been found in patients with pigmentary lesions of the lens and cornea. This condition has been a problem particularly with high doses (greater than 800 mg/day) of thioridazine; however, there are reports of its occurrence with other phenothiazines as well.

Prien and his colleagues[15] have addressed this problem in a well-controlled prospective study of 120 schizophrenic patients treated with chlor-

promazine. An increased incidence of corneal and lens changes was found among patients on high doses of chlorpromazine as compared to patients on low doses or on placebo. There was a high correlation between the development of photosensitivity and eye changes, but none of the study patients developed any deterioration in visual acuity over the nine-month period of the study. A similar study of trifluoperazine failed to disclose any significant eye changes.

Rasmussen's team[16] studied patients on chlorpromazine over 3 1/2 years to determine if there was any progression of pigmentary lesions either in the chlorpromazine group, the thioridazine group, or the control group. Visual acuity declined equally in both the experimental and control groups due to age. The authors concluded that eye changes with moderate dosage of chlorpromazine and thioridazine do occur but pose no threat to patients' eyesight.

Another complication of neuroleptic treatment which is rare but very serious is agranulocytosis. It appears more frequently with aliphatic phenothiazine derivatives and perhaps more with clozapine than with other drugs, but has been reported with all phenothiazines, thioxanthenes, butyrophenones, and dibenzoxazepines. It is thought to be due to suppression by the neuroleptic of DNA synthesizing enzymes in granulocyte precursors. In general, the risk of agranulocytosis decreases with a rise in milligram potency of the phenothiazine. Data compiled by the American Medical Association Council on Drugs between 1957 and 1967 indicated that susceptibility to agranulocytosis also increases with age and that age is an important factor in recovery. Of the 147 patients who developed agranulocytosis, none under the age of 30 died, but one third of those over 30 died. Race, too, seems to be a factor since no blood dyscrasias were found in black patients in several studies; moreover, one of the studies[17] indicated that obesity and chronic physical disability appear to increase the risk.

Agranulocytosis presents clinically with symptoms of infection unless it is discovered early by hematologic surveillance. Fever, sore throat, and weakness are seen along with marked lymphopenia and leukopenia. The marrow appears aplastic. Infection during this period is life threatening; however, if infection is avoided and the neuroleptic is discontinued, recovery occurs in two weeks.

Diagnosis has been attempted by some, with weekly white counts in all patients receiving neuroleptics. Pisciotta obtained 37,500 white blood cell counts in 6,300 inpatients and found only five cases of agranulocytosis.[18] Litvak and Kaelbling[19] obtained 40,000 white blood cell counts in 11,407 patients and found only five patients with counts of 2,000 white blood cells or less during the 15-year duration of their study. Only three of these patients ever developed any signs of infection. Clearly, the yield from routine white blood cell counts is minute, so if routine counts are to be made, they should be used only in suspected high-risk and older patients receiving chlorpromazine or thioridazine, and should be extended for no more than a few months. The best and most feasible way of preventing the consequences of agranulocytosis is to warn everyone: nursing staff, patients, and relatives to report sore throats and fevers immediately and then to get emergency white blood cell counts. For comparison purposes it is mandatory to have a baseline white blood cell count.

Treatment of this disorder consists of the immediate withdrawal of the offending agents. A careful check of the patient's other medication for agents known to affect hematopoiesis should also be made and these should also be discontinued. It must be remembered that this complication carries a grave prognosis. Vigorous and aggressive therapy is indicated. Cultures should be obtained, sensitivities should be tested, and infective agents should be treated with appropriate antibiotics.

Finally, the last of the idiosyncratic or toxic reactions, jaundice, occurs in less than one percent of patients, usually those on chlorpromazine. Clinically, the condition presents within the first two to four weeks of therapy. The urine may be dark; the alkaline phosphatase and serum bilirubin are elevated, but signs of hepatitis (fever, anorexia, hepatic tenderness) are usually not present though they may precede the onset of jaundice. Pathologically, the jaundice is of the obstructive type. Biopsy specimens show centrilobular cholestasis with little parenchymal damage. It is thought that the occurrence of jaundice is a hypersensitivity reaction. Eosinophilia with eosinophilic infiltration of the liver is always observed in these cases. Jaundice subsides when the

drug is stopped and will recur if the same drug is restarted. Often, switching to another neuroleptic medication will terminate the jaundice. Thus, many authorities believe that the occurrence of jaundice is not a contraindication to continued treatment.

Interaction of Antipsychotic Drugs and Other Drugs

The mentally ill patient on antipsychotic medication will often be exposed to other drugs from prescriptions by physicians or from self-medication. Antipsychotics interact with many drugs, and such interactions may alter the efficacy of therapy and possibly endanger the patient's safety or comfort. It is essential, therefore, that the family physician be aware of the more important drug interactions.

Because of anticholinergic activity, antipsychotics can interact with other anticholinergic agents producing a variety of symptoms, eg, glaucoma, xerostomia, ileus, hypotension, urinary retention, and cardiac irregularities. Additive effects from antiparkinsonian and other anticholinergic agents may also produce the "central anticholinergic syndrome" which has been previously mentioned. It is a toxic confusional state produced by the superimposition of an atropine-like psychosis upon the primary psychiatric disorder. Characteristically, its onset is heralded by the worsening of psychotic symptoms, disturbance of immediate memory, disorientation, visual hallucinations, and peripheral anticholinergic signs. The incidence of these reactions increases with age. Because they possess the highest anticholinergic activity of the antipsychotics, mesoridazine, thioridazine, and chlorpromazine are most often implicated in the production of unwanted atropinic effects. It should also be reiterated for emphasis that the antiparkinsonian agents along with other anticholinergic compounds reduce neuroleptic levels in plasma, possibly reducing therapeutic efficacy.[8] The mechanism of this action is not known.

Tricyclic antidepressants, which themselves possess anticholinergic properties, can also aggravate the atropinic effect of antipsychotics. Unlike antiparkinsonian agents, however, tricyclic antidepressants may raise the plasma levels of antipsychotics by a mechanism which is thought to involve inhibition of the hepatic microsomal system.[20] It was noted above that the symptoms of tardive dyskinesia worsen with a decrease in neuroleptic dose and transiently improve with an increase in dose. Hence, the physician must be aware that the effect of a tricyclic antidepressant on phenothiazine plasma level may lead to a level of the latter high enough to cause but also to mask tardive dyskinesia, until the antidepressant is withdrawn and a plasma level decrease in neuroleptic follows. The antipsychotics, in turn, raise the plasma levels of tricyclic antidepressants. This elevation may increase the antidepressant activity of the drug, since therapeutic efficacy bears some relationship to plasma drug levels. It should also be noted that the antipsychotic-tricyclic combination increases the risk of agranulocytosis, an expected effect whenever an antipsychotic is combined with other agents that suppress hematopoiesis.

Several other medications can affect the plasma levels of the antipsychotics. Estrogens have been shown to increase the serum concentrations of antipsychotics when given concurrently.[21] Barbiturates in contrast may decrease the serum levels of antipsychotics,[22] as may lithium.[23] The mechanisms of these interactions are not known.

The combination of antipsychotics and antihypertensive agents almost always produces additive hypotension. An important exception is guanethidine. Fann and his associates[24] found that the addition of chlorpromazine to guanethidine in hypertensive patients produced an increase in their diastolic blood pressures. Chlorpromazine inhibits the neuronal uptake of guanethidine and prevents its hypotensive effect by blocking access to its site of action. If chlorpromazine and false-transmitter antihypertensive agents are used together, the patient's blood pressure should be carefully monitered.

Due to alpha adrenergic-blocking activity, all antipsychotics interact with sympathomimetic agents, inhibiting the pressor effects. Norepinephrine, however, retains its ability to raise the blood pressure in combination with antipsychotics. Chlorpromazine may potentiate the warfarin anticoagulants. Finally, an adverse interaction of lithium and haloperidol was reported but is now believed to have been a coincidental true infectious encephalitis.[25]

The various side effects and interactions of neuroleptic drugs are nowhere more evident than in the geriatric patient population. The deployment of antipsychotic medications for the elderly patient requires special knowledge, experience, and care, particularly since this patient may be receiving several other medications. A variety of factors leads to an increase in both clinical activity and side effects of the drug. The amount of drug bound to plasma protein, as well as hepatic drug metabolism, may be reduced. The ratio of fat to parenchymal tissue is increased in the elderly, and lipophilic compounds including many neuroleptics tend to accumulate in fatty tissues. Thus, total body clearance of drug is slowed. In addition, the sensitivity of the central nervous system to drugs is usually increased.

These factors increase the likelihood of side effects from neuroleptic agents. The elderly patient shows increased susceptibility to neurological and cardiac side effects, and increased propensity for depression, paradoxical excitement, delirium, and assaultiveness. These side effects are frequently the result of the anticholinergic properties of antipsychotics, and are often worsened by the injudicious administration of antiparkinsonian agents. The latter should not be given prophylactically but only as needed, in small amounts, and only for as long as target symptomatology requires. Allergic reactions to antipsychotics, eg, agranulocytosis, also occur in greater frequency in older patients. Thus, the physician must monitor the geriatric patient closely for evidence of any undesirable drug effects.

Neuroleptic drugs should be prescribed in low dosages for elderly patients. Usually 30 percent of the dose for a young adult should be prescribed initially. Increase should be gradual and divided doses are preferable. Polypharmacy should be avoided. Absorption from the gastrointestinal tract may be altered in the elderly and the physician, after trying a liquid preparation, might well try the parenteral route but with reduced doses. The titration of a new pharmacological regimen may be better achieved in an inpatient setting. Treatment should be monitored with frequent physical, mental status, and laboratory evaluations, and persons in the patient's natural habitat should be educated as to the specific drugs given, the therapeutic objectives, and probable side effects. In this manner, antipsychotic treatment of the elderly, though more complex than treatment of other age groups, may be successfully accomplished.

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